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Triple Antiplatelet Therapy During Percutaneous Coronary Intervention Is Associated With Improved Outcomes Including One-Year Survival

Results From the Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (TARGET)

Albert W. Chan, MD,* David J. Moliterno, MD,† Peter B. Berger, MD,‡ Gregg W. Stone, MD,§ Peter M. DiBattiste, MD,‖ Steven L. Yakubov, MD,¶ Shelly K. Sapp, MS,# Kathy Wolski, MPH,# Deepak L. Bhatt, MD,† Eric J. Topol, MD,† for the TARGET Investigators**

New Orleans, Louisiana; Cleveland and Columbus, Ohio; Rochester, Minnesota; New York, New York; and West Point, Pennsylvania

OBJECTIVES We sought to examine if clopidogrel treatment initiated before coronary stenting improved clinical outcomes among patients receiving aspirin and a glycoprotein (GP) IIb/IIIa inhibitor.

BACKGROUND Antiplatelet therapy plays a pivotal role in contemporary percutaneous coronary interventions (PCI).

METHODS Outcomes among 4,809 patients randomized to tirofiban or abciximab during PCI with stent placement were compared according to whether they received 300 mg of clopidogrel before PCI (93.1%) versus immediately after the procedure.

RESULTS The 30-day primary composite end point (death, myocardial infarction [MI], or urgent target vessel revascularization [TVR]) was lower among clopidogrel-pretreated patients (6.6% vs. 10.4%, p = 0.009), mainly because of reduction of MI (6.0% vs. 9.5%, p = 0.012). The benefit of clopidogrel pretreatment was sustained at six months (death, MI, any TVR: 14.6% vs. 19.8%, HR = 0.71, p = 0.010), and this was due mainly to lowering of death and MI (7.8% vs. 13.0%, p = 0.001). At one year, clopidogrel pretreatment was associated with a lower mortality rate (1.7% vs. 3.6%, p = 0.011). Because clopidogrel pretreatment was not randomized, multivariable and propensity analyses were performed. After adjusting for baseline heterogeneity, clopidogrel pretreatment was an independent predictor for death or MI at 30 days (HR = 0.63, p = 0.012) and at six months (HR = 0.61, p = 0.003), and survival at one year (HR = 0.53, p = 0.044). No excess in 30-day bleeding events was noted with clopidogrel pretreatment.

CONCLUSIONS Among patients undergoing coronary stent placement with aspirin and a GP IIb/IIIa inhibitor, clopidogrel pretreatment is associated with a reduction of death and MI irrespective of the type of GP IIb/IIIa inhibitor used. (J Am Coll Cardiol 2003;42:1188–95) © 2003 by the American College of Cardiology Foundation

Antiplatelet therapy plays a pivotal role in percutaneous coronary interventions (PCI). The use of aspirin during coronary balloon angioplasty reduces the incidence of acute thrombotic complications (1–3). When added to aspirin, intravenous glycoprotein (GP) IIb/IIIa receptors further improve clinical outcome during elective, urgent, and emergency PCI (4–10). The administration of ticlopidine after coronary stenting also improves clinical outcome (11–18). In a subanalysis of the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial (19), ticlopidine given before PCI was associated with a reduction of subsequent major adverse cardiac events during the first year. However, this benefit was evident only among patients randomly assigned to placebo and not among those patients receiving the GP IIb/IIIa inhibitor abciximab.

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Clopidogrel is a selective, irreversible adenosine diphosphate (ADP) receptor antagonist (20). It has a more rapid platelet anti-aggregatory effect than ticlopidine, and achieves near maximal platelet inhibition within 2 to 6 h using a 300 mg oral loading dose (21–23). Given after PCI, the combination of aspirin and clopidogrel appears to have a superior safety profile as compared with aspirin plus ticlopidine (24–28). In a recent substudy from the Clopidogrel in Unstable Angina to Prevent Recurrent Events trial (PCI-CURE) (29), clopidogrel treatment before PCI (with or without stent placement) was associated with improved outcome, though less than one-fourth of the patients received IIb/IIIa inhibitors. Because GP IIb/IIIa antagonists provide potent inhibition of platelet aggregation and

From the *Department of Cardiology, Ochsner Clinic Foundation, New Orleans, Louisiana; †Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio; ‡Division of Cardiology, Mayo Clinic Foundation, Rochester, Minnesota; §Lenox Hill Heart and Vascular Institute, New York, New York; ‖Merck, West Point, Pennsylvania; ¶Riverside Methodist Hospital, Columbus, Ohio; and #Department of Biostatistics and Epidemiology, The Cleveland Clinic Foundation, Cleveland, Ohio. The TARGET study was supported by Merck, Inc., West Point, Pennsylvania. Dr. DiBattiste is an employee of Merck. **For the full list of TARGET investigators, please refer to N Engl J Med 2001;344:1888–94.

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Abbreviations and Acronyms

ACS	= acute coronary syndrome
ADP	= adenosine diphosphate
CREDO	= Clopidogrel for Reduction of Events During Observation
EPISTENT	= Evaluation of Platelet IIb/IIIa Inhibitor for Stenting
GOLD	= Assessing Ultegra-AU Study
GP	= glycoprotein
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
PCI-CURE	= PCI substudy of the Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial
TIMI	= Thrombolysis In Myocardial Infarction
TVR	= target vessel revascularization

have become a standard pharmacologic adjunct in contemporary PCI, whether clopidogrel pretreatment provides important additional benefits among patients receiving IIb/IIIa inhibitors remains uncertain. Therefore, we examined the impact of clopidogrel pretreatment among patients in the Do Tirofiban and ReoPro Give Similar Efficacy Outcome Trial (TARGET) (30).

METHODS

Study protocol. The design and methods of TARGET have been previously detailed (30,31). In brief, 4,809 patients undergoing elective or urgent PCI-stent of native coronary vessels or bypass grafts were enrolled between December 1999 and August 2000 in 149 hospitals in North America, Australia, and Europe. Patients were randomized in a double-blind, double-dummy fashion to receive a bolus and infusion of either abciximab or tirofiban. All patients received 250 to 500 mg of aspirin within 24 h before the procedure and 75 to 325 mg/day following the procedure. A loading dose of 300 mg of clopidogrel at least 2 to 6 h before the procedure was recommended. Alternatively, the same dose of clopidogrel could be given just before the PCI procedure if it were performed immediately following diagnostic angiography. The timing of clopidogrel administration was at the interventional cardiologists' discretion. Patients who received clopidogrel before either abciximab or tirofiban was given were categorized into the clopidogrel pretreatment group. Otherwise, a 300-mg loading dose of clopidogrel was to be given as early as possible after the procedure. Clopidogrel was continued for 30 days after PCI at a dose of 75 mg daily. At the time of procedure, heparin was administered to achieve an activated clotting time $\geq$250 s. Interventional procedures were performed as per institutional standard.

Study end points. The primary end point of TARGET was the composite of death, nonfatal myocardial infarction (MI), or urgent TVR within 30 days of the index procedure. Prespecified secondary end points included the composite of death, nonfatal MI, or any TVR at six months and mortality at one year. Treatment assignment remained blinded to one year. The definition of MI during index hospitalization and to six months was described previously (30). Target vessel revascularization was defined as any repeat revascularization of the vessel treated during the index procedure. For the safety analysis, the end points of major and minor bleeding were defined using the Thrombolysis In Myocardial Infarction (TIMI) criteria (32). End points were reported by investigators, and were reviewed and adjudicated by an independent Clinical Events Committee.

Statistical analysis. All patients were categorized according to whether they received pretreatment with clopidogrel or not. The time of first clopidogrel administration was recorded, and subanalysis was performed separating patients into pretreatment intervals: no pretreatment; treatment 0 to 2 h, 2 to 6 h, or >6 h before PCI (time zero defined as when IIb/IIIa inhibitor bolus was given). The demographic, procedural, and safety data are reported as percentages for discrete variables, and as means $\pm$ 1 SD for continuous variables. Comparisons of the baseline characteristics between clopidogrel pretreatment and no pretreatment were made by means of chi-square statistics for categorical variables and Mann-Whitney-Wilcoxon tests for continuous variables. Fisher's exact test was used to compare infrequent events such as major and minor bleeding. Kaplan-Meier methods were used to estimate end points at 30 days, 6 months, and 1 year, and log-rank tests were used to compare the clopidogrel pretreatment and no pretreatment groups.

Because the timing of clopidogrel administration relative to the PCI procedure was not randomized, a propensity analysis was performed (33) to adjust for potential bias inherent in treating patients with clopidogrel before rather than following PCI. Based on the individual demographic and preprocedural clinical characteristics, a propensity score was developed for each patient using a multivariable logistic regression model in order to estimate the probability of clopidogrel pretreatment. Covariates that were tested in the model included demographic characteristics (age, gender, race, body mass index), cardiovascular risk factors (cigarette smoking, hypertension, diabetes, hypercholesterolemia, and family history of coronary artery disease), cardiovascular and major noncardiac comorbidities (prior history of coronary bypass, PCI, MI, heart failure, stroke, peripheral arterial disease, gastrointestinal disorders, and bleeding diathesis), acuity of presentation (recent Q-wave MI, non–Q-wave MI, unstable angina, and stable angina), and concomitant medication use (aspirin, angiotensin-converting enzyme inhibitors, beta-blockers, calcium-receptor antagonist, lipid-lowering agent, nitrates, anti-inflammatory agents, anti-ulcerants, insulin, and hypoglycemic agents). To examine the impact of clopidogrel pretreatment on outcome, the propensity score was entered into the Cox proportional hazards model as a continuous variable along with potential covariates that might affect outcome. These variables in-

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cluded those entered into the propensity score model, and the procedural variables (assigned study drug, prior heparin use, number of diseased vessels, target vessel(s), lesion length, multivessel PCI, pre-TIMI flow, U.S. vs. non-U.S. enrollment). A p value of <0.05 was considered statistically significant in all analyses.

RESULTS

Of the 4,809 patients enrolled, 4,477 (93.1%) were given clopidogrel before PCI. Baseline clinical characteristics of the two groups are shown in Table 1. Of note, the two groups were similar regarding cardiovascular risk profile, the prevalence of comorbidities, and indication for coronary revascularization. Compared with patients who did not receive clopidogrel before PCI, clopidogrel-pretreated patients were more likely to receive aspirin, beta-blockers, calcium-channel blockers, and lipid-lowering therapy before their procedures. Among the patients who received pretreatment, 2,535 patients (56.6%) received the loading dose within 2 h before procedures, 1,216 patients (27.2%) within 2 to 6 h, and 726 patients (16.2%) for >6 h before the index procedure. The mean duration from clopidogrel administration to initiation of PCI was 2.1 h.

30-day outcomes. The primary composite end point of death, MI, or urgent TVR at 30 days occurred in 10.4% of patients without pretreatment and in 6.6% of patients with clopidogrel pretreatment ($p = 0.009$, Table 2). The benefit of clopidogrel pretreatment was predominantly due to a reduction in MI (9.5% vs. 6%, $p = 0.012$). There was no significant difference in the triple end point event rates between patients who received pretreatment for 0 to 2 h and those who were pretreated for 2 to 6 h (6.5% vs. 7.7%, respectively; $p = 0.198$). Compared with patients who did not receive clopidogrel until after PCI, those who were pretreated 0 to 6 h before the procedure had a 34% lower composite event rate (6.9% vs. 10.4%, $p = 0.021$). Furthermore, as compared with those who were pretreated for <6 h, patients who were clopidogrel-loaded for >6 h before PCI had a 29% lowering in 30-day events (6.9% vs. 4.9%, $p = 0.045$); this difference was due mainly to fewer MI events (6.3% vs. 4.2%, $p = 0.028$).

Figure 1 illustrates the rates of primary end point according to clopidogrel pretreatment and IIb/IIIa drug assignment. When given to patients randomized to tirofiban therapy, clopidogrel pretreatment relatively reduced the 30-day event rate by 43%, from 12.8% to 7.3% ($p = 0.017$). Likewise, patients who were pretreated with clopidogrel and received abciximab had a 30% relative reduction in the composite event rate (from 8.4% to 5.9%, $p = 0.168$) compared with abciximab without clopidogrel pretreatment. Whereas the overall TARGET study showed a 26% relative risk reduction in primary end point with abciximab as compared with tirofiban, the superiority of abciximab was attenuated among patients who received clopidogrel pretreatment (Table 3).

Table 1. Baseline Clinical and Target Lesion Characteristics of Patients Who Were Pretreated and Those Who Were Not Pretreated With Clopidogrel

	Clopidogrel Pretreatment (n = 4,477)	No Clopidogrel Pretreatment (n = 332)	p
Age, yrs	62.3 ± 10.9	62.5 ± 11.3	0.954
Female, %	26.4	28.3	0.441
Weight, kg	86.0 ± 17.6	87.6 ± 18.5	0.121
Caucasian, %	91.4	88.0	0.034
Risk factors, %			
Cigarette smoking	21.8	24.2	0.306
Diabetes mellitus	23.3	22.0	0.579
Hypertension	64.5	68.9	0.110
Hypercholesterolemia	75.1	72.0	0.214
Family history of coronary artery disease	54.7	53.1	0.577
Medical history, %			
Coronary bypass grafting	17.2	13.3	0.064
Prior PCI	29.7	27.5	0.404
Heart failure	9.7	11.5	0.292
Myocardial infarction	39.6	36.6	0.267
Prior stroke	2.7	2.4	0.722
Peripheral arterial disease	9.6	11.5	0.265
Gastrointestinal disorders	23.9	24.8	0.719
Bleeding disorders	0.8	1.2	0.330
Medications, %			
Aspirin (within 24 h)	97.3	93.6	< 0.001
ACE inhibitors	36.9	32.5	0.113
Beta-blockers	66.0	57.8	0.003
Calcium-channel antagonists	31.7	24.4	0.006
Lipid-lowering agents	60.7	48.8	< 0.001
Nitrates	59.5	58.7	0.789
Thombolytics during index admission	5.3	4.2	0.395
Anti-inflammatory agents	15.1	16.9	0.393
Anti-ulcerants	32.5	29.8	0.310
Insulin	8.2	8.1	0.944
Oral hypoglycemic agents	16.6	15.4	0.573
Randomized to abciximab, %	49.8	54.2	0.123
Indication for PCI, %			0.541
Q-wave MI	5.5	5.4	
Non–Q-wave MI	10.3	9.3	
Unstable angina	46.9	51.5	
Stable angina and others	37.3	33.8	
Lesion location			
Left anterior descending artery	42.6	42.3	0.920
Circumflex artery	28.1	29.3	0.643
Right coronary artery	37.3	38.1	0.776
Left main coronary artery	1.3	1.8	0.454
Bypass graft	6.1	5.4	0.625
Severity of stenosis before PCI	87.6 ± 9.7%	88.4 ± 9.8%	0.117
Lesion length, %			0.912
<10 mm	24.9	25.2	
10–20 mm	59.2	58.2	
>20 mm	15.9	16.7	
Left ventricular ejection fraction			0.244
>50%	72.6	73.1	
30%–50%	25.0	22.9	
<30%	2.5	4.0	

ACE = angiotensin-converting enzyme; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2. Clinical End Points at 30 Days, 6 Months, and 1 Year According to Clopidogrel Pretreatment

	Clopidogrel Pretreatment n = 4,477 (%)	No Clopidogrel Pretreatment n = 332 (%)	Hazard Ratio (95% CI)	p
30 days				
Death	19 (0.4)	3 (0.9)	0.46 (0.14–1.55)	0.196
MI	265 (6.0)	31(9.5)	0.62 (0.43–0.91)	0.012
Death/MI	277 (6.2)	33 (10.1)	0.61 (0.43–0.88)	0.007
Urgent TVR	33 (0.7)	3 (0.9)	0.80 (0.25–2.61)	0.711
Death, MI, or urgent TVR	292 (6.6)	34 (10.4)	0.63 (0.44–0.89)	0.009
6 months				
Death	43 (1.0)	8 (2.6)	0.39 (0.18–0.82)	0.010
MI	315 (7.1)	35 (10.7)	0.65 (0.46–0.92)	0.015
Death/MI	344 (7.8)	42 (13.0)	0.59 (0.43–0.81)	0.001
Any TVR	373 (8.7)	29 (9.4)	0.92 (0.63–1.34)	0.647
Death, MI, or any TVR	638 (14.6)	63 (19.8)	0.71 (0.55–0.92)	0.010
1 year mortality	76 (1.7)	12 (3.6)	0.46 (0.25–0.85)	0.011

Hazard ratios and p values are unadjusted.
CI = confidence interval; MI = myocardial infarction; TVR = target vessel revascularization.

Six-month outcomes. Clopidogrel pretreatment was associated with a reduction in the composite of death, MI, or any TVR at six months (14.6% vs. 19.8%, p = 0.010), mainly due to a reduction in the composite of death or nonfatal MI (Table 2). The death or MI composite was 38% lower among those given clopidogrel 0 to 6 h before PCI as opposed to after the procedure (8.1% vs. 13.0%, p = 0.003). This rate was an additional 26% lower for patients pretreated >6 h before PCI (6.0% vs. 8.1%, p = 0.051). The impact of clopidogrel pretreatment appeared more evident among patients randomized to tirofiban than abciximab, and this benefit predominantly occurred as a reduction in the death or MI composite (Table 3, Fig. 2). Comparing clopidogrel pretreatment with no pretreatment, the death or MI composite was reduced from 15.5% to 8.4% (hazard ratio [HR] = 0.54, p = 0.004) in the tirofiban group and from 10.9% to 7.2% (HR = 0.66, p = 0.076) in the abciximab group.

One-year mortality. Clopidogrel given before the index procedure was associated with a significant mortality reduction within the first year (1.7% vs. 3.6%, HR = 0.47, p = 0.011). This was mainly due to the reduction in mortality in the tirofiban group (1.8% vs. 4.6%, p = 0.012), though a small benefit may have existed in the abciximab group (1.7%

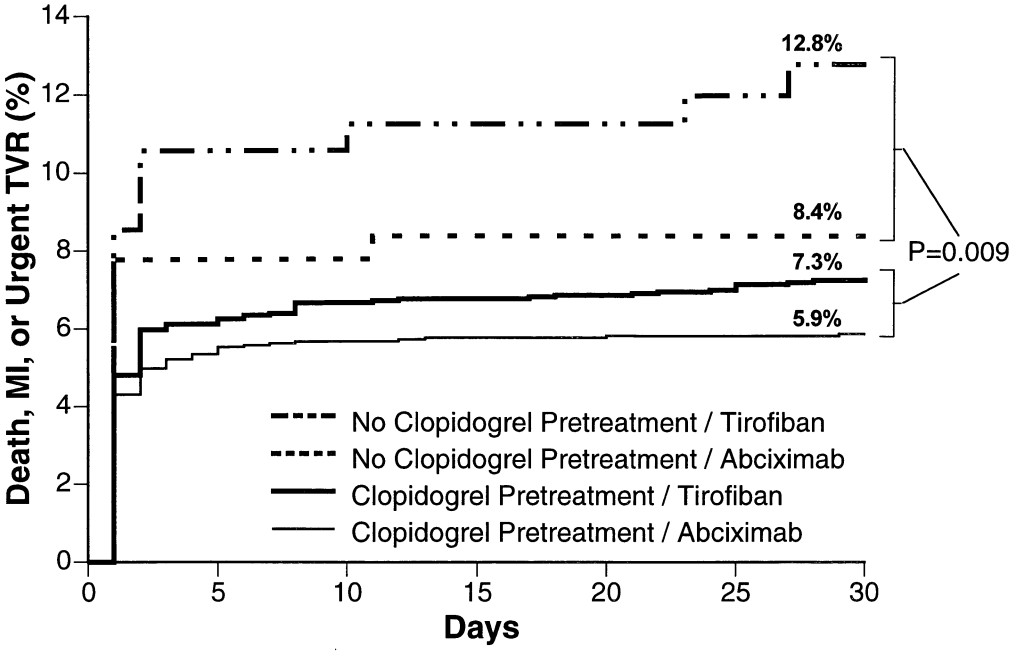

Figure 1. Kaplan-Meier curves of 30-day composite of death, nonfatal myocardial infarction (MI), and urgent target vessel revascularization (TVR) in patients according to clopidogrel pretreatment and assignment of glycoprotein IIb/IIIa inhibitors. The clinical benefit of clopidogrel pretreatment was present regardless of which IIb/IIIa agent was used. Abciximab was superior to tirofiban in terms of 30-day composite end point; however, the extent appears attenuated in the presence of clopidogrel pretreatment.

Table 3. Influence of Clopidogrel Pretreatment on Relative Efficacy of Tirofiban Versus Abciximab on Various End Points

	Clopidogrel Pretreatment (n = 4,477)				No Clopidogrel Pretreatment (n = 332)			
	Abciximab n = 2,231 (%)	Tirofiban n = 2,246 (%)	Hazard Ratio* (95% CI)	p	Abciximab n = 180 (%)	Tirofiban n = 152 (%)	Hazard Ratio* (95% CI)	p
30 days								
Death	8 (0.4)	11 (0.5)	0.73 (0.29–1.81)	0.497	2 (1.2)	1 (0.7)	1.72 (0.16–20.00)	0.655
MI	118 (5.3)	147 (6.6)	0.81 (0.63–1.03)	0.080	13 (7.2)	18 (12.1)	0.61 (0.30–1.23)	0.167
Death/MI	124 (5.6)	153 (6.9)	0.81 (0.64–1.03)	0.087	14 (7.8)	19 (12.8)	0.62 (0.31–1.23)	0.170
Urgent TVR	15 (0.7)	18 (0.8)	0.83 (0.42–1.67)	0.609	1 (0.6)	2 (1.4)	0.42 (0.04–4.76)	0.470
Death, MI, or urgent TVR	130 (5.9)	162 (7.3)	0.81 (0.64–1.01)	0.065	15 (8.4)	19 (12.8)	0.67 (0.33–1.32)	0.234
6 months								
Death	21 (1.0)	22 (1.0)	0.96 (0.53–1.75)	0.891	4 (2.4)	4 (2.9)	0.91 (0.23–3.57)	0.883
MI	143 (6.5)	172 (7.8)	0.83 (0.67–1.04)	0.108	16 (9.1)	19 (12.6)	0.71 (0.37–1.39)	0.324
Death/MI	159 (7.2)	185 (8.4)	0.86 (0.69–1.06)	0.167	19 (10.9)	23 (15.5)	0.70 (0.38–1.30)	0.856
Any TVR	193 (9.0)	180 (8.3)	1.08 (0.88–1.32)	0.470	15 (9.3)	14 (9.5)	0.96 (0.46–2.00)	0.909
Death, MI, or any TVR	314 (14.4)	324 (14.7)	0.97 (0.83–1.34)	0.688	31 (18.3)	32 (21.6)	0.83 (0.51–1.35)	0.459
1-year mortality	37 (1.7)	39 (1.8)	0.95 (0.61–1.49)	0.840	5 (2.8)	7 (4.6)	0.61 (0.19–1.92)	0.390

*Refers to the unadjusted hazard ratios for abciximab vs. tirofiban.
Abbreviations as in Table 2.

vs. 2.8%, p = 0.257). For patients who did not receive clopidogrel pretreatment, abciximab administration was associated with a numerically lower but statistically similar mortality rate at one year compared with tirofiban (2.8% vs. 4.6%, p = 0.390).

Multivariable analysis. Within the propensity score analysis, variables that independently predicted the use of clopidogrel before PCI were (in descending order) prescription of lipid-lowering agents, concomitant aspirin use and history of angina. The following variables were also included in the logistic model using intersections statistics to develop the final propensity score: BMI >30, race, hypertension, and use of prior medications such as angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel blockers. The goodness-of-fit for the propensity score as assessed by the *c*-statistic was 0.64. Using Cox proportional hazards modeling to adjust for potential variables and the propensity of prescribing clopidogrel before the procedure, clopidogrel pretreatment remained an independent predictor for a lower composite of death or MI at 30 days and six months. Other independent correlates for death or MI at 30 days and 6 months are provided in Table 4.

Not surprisingly, the strongest predictors for outcome included advanced age, acuity of disease (acute coronary syndrome [ACS]), and extent of atheroma (lesion length and number of vessels revascularized). Adding statistical interactions to several proportional hazard models, clopidogrel continued to provide independent predictive value.

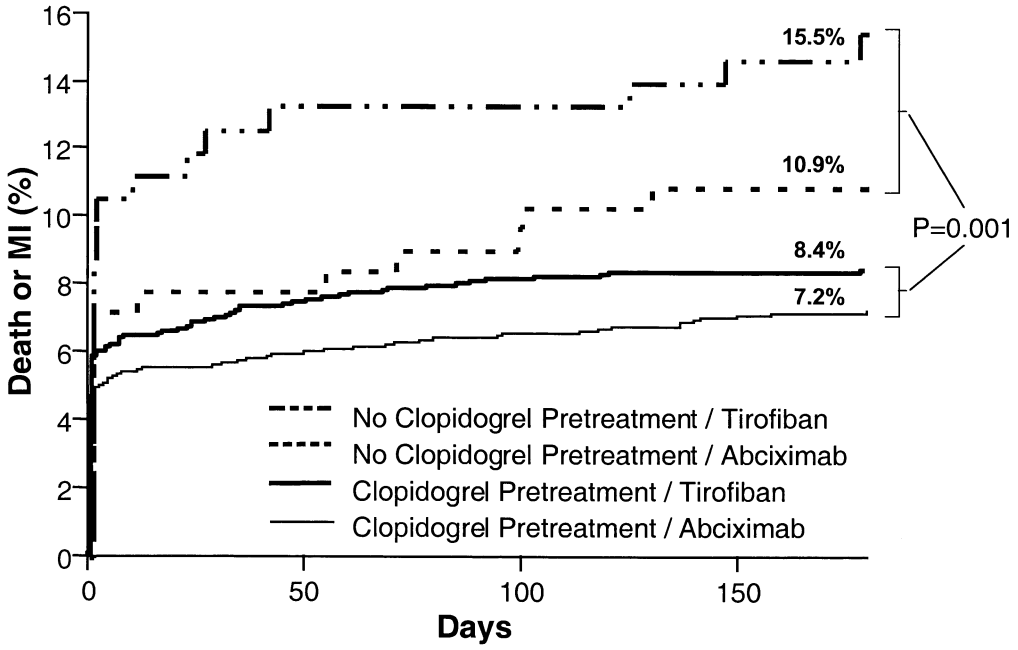

Figure 2. Kaplan-Meier curves of composite of death and nonfatal myocardial infarction (MI) to six months, based on the use of clopidogrel pretreatment and assignment of glycoprotein IIb/IIIa inhibitors.

Table 4. Independent Predictors for Death or MI After Coronary Stenting

Characteristics	Hazard Ratio	95% Confidence Interval	p
30 days			
Clopidogrel pretreatment	0.63	0.43–0.90	0.012
RCA intervention	0.75	0.59–0.95	0.017
Abciximab vs. tirofiban	0.80	0.64–1.00	0.048
Propensity score	0.99	0.72–1.38	0.979
Age ≥ 65 years	1.53	1.22–1.91	< 0.001
Multivessel PCI	1.60	1.22–2.10	0.001
Maximal lesion length*	1.86	1.55–2.24	< 0.001
6 months			
Clopidogrel pretreatment	0.61	0.44–0.84	0.003
RCA intervention	0.78	0.63–0.97	0.022
Propensity score	0.99	0.75–1.35	0.977
Age ≥ 65 years	1.31	1.07–1.61	0.008
Acute coronary syndrome	1.39	1.10–1.75	0.005
Heart failure	1.51	1.14–2.00	0.005
Multivessel PCI	1.51	1.18–1.93	0.001
Maximal lesion length*	1.68	1.43–1.98	< 0.001

*Classified as <10 mm vs. 10–20 mm vs. >20 mm.
MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

Interestingly, in one analysis, the use of antidepressants contributed to the overall model (chi-squared = 6), and when adding the interaction term preprocedural clopidogrel × antidepressant use, the separate contribution of clopidogrel pretreatment was decreased whereas the contribution of antidepressants was increased. At one-year follow-up, clopidogrel pretreatment remained an independent predictor for survival (HR = 0.53; 95% CI, 0.29 to 0.98; p = 0.044) after adjusting for the study drug treatment, age, gender, body mass index, presentation acuity, cardiac and vascular comorbidities, cardiovascular risk factors, bleeding disorders, and medication use.

Bleeding. The incidence of major and minor bleeding, and frequency of transfusion according to clopidogrel pretreatment, are listed in Table 5. The frequency of these complications was low, and there was no significant increase in bleeding events among patients treated with clopidogrel before undergoing PCI with adjunctive GP IIb/IIIa inhibitors.

Table 5. Incidence of Bleeding and Transfusion During Index Hospitalization

	Clopidogrel Pretreatment (n = 4,477)	No Clopidogrel Pretreatment (n = 332)	p
Major or minor bleeding, %	4.3	3.9	0.718
Major bleeding, %	0.8	0.9	0.754
Minor bleeding, %	3.6	3.3	0.821
Transfusion, %			
Packed red blood cells	1.3	0.9	0.800
Platelet	0.4	0.9	0.191
Plasma	0.2	0.3	0.475

DISCUSSION

Among PCI patients undergoing stent placement with adjunctive aspirin and a GP IIb/IIIa inhibitor, clopidogrel administered as an oral loading dose before the procedure was associated with superior clinical outcome, which was evident within 24 to 48 h after the procedure and was sustained at 6 months. Although the outcome with >6 h of pretreatment was more favorable than that of 0 to 6 h of pretreatment, clopidogrel loading within 6 h before the procedure was also associated with significantly better outcome as compared with no pretreatment. Clopidogrel pretreatment was predominantly associated with a reduction in ischemic events (MI), though its benefit appears to extend to mortality reduction at one year. These associations remained markedly significant following adjustment for baseline clinical and procedural characteristics, as well as the propensity for receiving preprocedural clopidogrel. The observations remained significant even when broadening the composite six-month outcome to include target vessel revascularization.

The efficacy of thienopyridine pretreatment before PCI has been reported (19,29,34). In the EPISTENT trial (19), pretreatment with a thienopyridine (ticlopidine) was associated with a reduction of major adverse cardiac events, though the benefit was not seen among patients randomized to IIb/IIIa inhibition. In the PCI-CURE study (29), the duration of clopidogrel pretreatment was markedly longer than in the current study (days versus hours), but cardiac enzymes were not routinely measured postprocedure. The presence of an interaction between clopidogrel pretreatment and IIb/IIIa inhibitor use could not be readily assessed because IIb/IIIa inhibitors were administered to a minority of PCI-CURE patients. The results of the Clopidogrel for Reduction of Events During Observation (CREDO) trial showed that clopidogrel pretreatment before PCI reduced a 28-day composite of death, MI, or urgent revascularization 18.5% (from 8.3% to 6.8%, p = 0.23), though the benefit did not reach statistical significance perhaps owing to sample size (35). However, similar to the PCI-CURE trial, less than one-fourth of the CREDO patients received planned GP IIb/IIIa inhibitor treatment, and a similarly small percentage of patients were treated with IIb/IIIa therapy as part of a bailout strategy. Consistent with the early report from CREDO, we observed the lowest adverse event rate among those with >6 h of clopidogrel pretreatment. Given the large sample size in TARGET, it is impressive that treatment with clopidogrel prior to coronary stenting was associated with incremental benefit in the presence of both aspirin and a IIb/IIIa inhibitor. This benefit seems extraordinary and likely reflects the importance of inflammation and platelets in PCI associated with vascular injury (36).

The mechanism of benefit with clopidogrel pretreatment deserves particular attention. When combined with aspirin therapy, clopidogrel provides synergistic antiplatelet effects

via concurrent inhibition of ADP and thromboxane A_2 pathways (37,38). Based on the results from the Assessing Ultegra-AU (GOLD) study (39), optimal PCI outcome regarding death or MI was observed with ≥95% inhibition of platelet aggregation at 10 min after initiation of therapy. Interestingly, using ADP-induced platelet aggregation testing, the tirofiban regimen used in TARGET produced <70% platelet inhibition during the first 60 min of procedure, in contrast to abciximab, which consistently achieved >90% inhibition during this time (40,41). As such, clopidogrel pretreatment may lower the risk of myocardial necrosis during the window of vulnerability following the tirofiban bolus and before the drug infusion can achieve adequate plasma levels (40,42,43). Even among abciximab-receiving patients with PCI, the current analysis suggests that clopidogrel pretreatment provides benefit.

Additionally, it is possible that a benefit of clopidogrel pretreatment is separately related to a reduction in platelet activation and inflammation. Elevated C-reactive protein (CRP) level has been linked to the risk of cardiovascular death and MI after PCI (44,45). This association was blunted in the presence of clopidogrel pretreatment (46), implying that patients with elevated baseline CRP may derive particular benefit from clopidogrel pretreatment. Indeed, formation of platelet-leukocyte aggregates was reduced by clopidogrel through lowering CD62 expression in an in vitro model (47), suggestive of a link between platelet activation and inflammation. Although patients with ACS are more likely to have an associated heightened inflammatory state, both ACS and non-ACS patients received similar benefit from clopidogrel pretreatment in the TARGET trial (48).

Study limitations. Clopidogrel pretreatment in this study was not randomized. Despite the use of contemporary statistical methods to adjust for imbalances between the pretreatment and no pretreatment groups, unmeasured confounders might have influenced the decision regarding the timing of clopidogrel administration (selection bias), and the intermediate goodness-of-fit of the propensity model (C-statistic 0.64) may reflect this. Alternatively, the model's fit may only be modest because the covariates were already fairly balanced between the groups. It is worth noting that the major determinants of early and intermediate outcome after PCI, such as age, left ventricular function, indication for procedure, and diabetic status were similar between the two study groups. As noted in Table 4, the propensity score itself was not independently predictive of outcome. This suggests that decisions regarding pretreatment with clopidogrel were not systematically biased according to baseline prognostic profiles. Finally, the duration of clopidogrel therapy before the index procedure was variable among patients. The quick onset of effect for the 300-mg bolus dosing reduces the effect of dose duration, although patients treated more than 6 h in advance had the best outcome. However, by including all patients who received clopidogrel regardless of how soon before beginning PCI, our observations should only underestimate the effect of clopidogrel pretreatment.

Conclusions. Our analysis suggests that in addition to platelet inhibition provided by aspirin and GP IIb/IIIa inhibitors, administration of clopidogrel before coronary stenting further reduces ischemic complications during both elective and urgent PCI procedures. Even a relatively brief period of clopidogrel pretreatment, such as a loading dose several hours before PCI, is associated with improved outcomes. Pretreatment for >6 h was associated with even greater antithrombotic protection and was found to be safe. This triple therapy antiplatelet regimen should be considered for all PCI-stent patients.

Reprint requests and correspondence: Dr. David J. Moliterno, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Desk F25, Cleveland, Ohio 44195. E-mail: molited@ccf.org.

REFERENCES

1. Barnathan ES, Schwartz JS, Taylor L, et al. Aspirin and dipyridamole in the prevention of acute coronary thrombosis complicating coronary angioplasty. Circulation 1987;76:125–34.
2. Schwartz L, Bourassa MG, Lesperance J, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med 1988;318:1714–9.
3. Savage MP, Goldberg S, Bove AA, et al. Effect of thromboxane A2 blockade on clinical outcome and restenosis after successful coronary angioplasty. Multi-Hospital Eastern Atlantic Restenosis Trial (M-HEART II). Circulation 1995;92:3194–200.
4. Topol EJ, Califf RM, Weisman HF, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. The EPIC Investigators. Lancet 1994;343:881–6.
5. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. Lancet 1997;349:1429–35.
6. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. Lancet 1997;349:1422–8.
7. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689–96.
8. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. Circulation 1997;96:1445–53.
9. Lincoff AM, Califf RM, Moliterno DJ, et al. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. N Engl J Med 1999;341:319–27.
10. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037–44.
11. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9.
12. Urban P, Macaya C, Rupprecht HJ, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients: the Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS). Circulation 1998;98:2126–32.
13. Rupprecht HJ, Darius H, Borkowski U, et al. Comparison of antiplatelet effects of aspirin, ticlopidine, or their combination after stent implantation. Circulation 1998;97:1046–52.

14. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med 1998; 339:1665–71.
15. Schuhlen H, Kastrati A, Pache J, Dirschinger J, Schomig A. Sustained benefit over four years from an initial combined antiplatelet regimen after coronary stent placement in the ISAR trial. Intracoronary Stenting and Antithrombotic Regimen. Am J Cardiol 2001;87:397–400.
16. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.
17. Schuhlen H, Kastrati A, Pache J, Dirschinger J, Schomig A. Incidence of thrombotic occlusion and major adverse cardiac events between two and four weeks after coronary stent placement: analysis of 5,678 patients with a four-week ticlopidine regimen. J Am Coll Cardiol 2001;37:2066–73.
18. Berger PB, Mahaffey KW, Meier SJ, et al. Safety and efficacy of only 2 weeks of ticlopidine therapy in patients at increased risk of coronary stent thrombosis: results from the Antiplatelet Therapy alone versus Lovenox plus Antiplatelet therapy in patients at increased risk of Stent Thrombosis (ATLAST) trial. Am Heart J 2002;143:841–6.
19. Steinhubl S, Ellis S, Wolski K, Lincoff A, Topol E, for the EPISTENT Investigators. Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events. Data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) Trial. Circulation 2001;103:1403–9.
20. Geiger J, Brich J, Honig-Liedl P, et al. Specific impairment of human platelet P2Y(AC) ADP receptor-mediated signaling by the antiplatelet drug clopidogrel. Arterioscler Thromb Vasc Biol 1999;19:2007–11.
21. Thebault JJ, Kieffer G, Cariou R. Single-dose pharmacodynamics of clopidogrel. Semin Thromb Hemost 1999;25:3–8.
22. Savcic M, Hauert J, Bachmann F, Wyld PJ, Geudelin B, Cariou R. Clopidogrel loading dose regimens: kinetic profile of pharmacodynamic response in healthy subjects. Semin Thromb Hemost 1999;25: 15–9.
23. Cadroy Y, Bossavy JP, Thalamas C, Sagnard L, Sakariassen K, Boneu B. Early potent antithrombotic effect with combined aspirin and a loading dose of clopidogrel on experimental arterial thrombogenesis in humans. Circulation 2000;101:2823–8.
24. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. Circulation 1999;99:2364–6.
25. Berger PB, Bell MR, Rihal CS, et al. Clopidogrel versus ticlopidine after intracoronary stent placement. J Am Coll Cardiol 1999;34: 1891–4.
26. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, Investigators FT. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting: the clopidogrel aspirin stent international cooperative study (CLASSICS). Circulation 2000;102:624–9.
27. Taniuchi M, Kurz HI, Lasala JM. Randomized comparison of ticlopidine and clopidogrel after intracoronary stent implantation in a broad patient population. Circulation 2001;104:539–43.
28. Bhatt DL, Bertrand ME, Berger PB, et al. Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. J Am Coll Cardiol 2002;39:9–14.
29. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long- term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358:527–33.
30. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. N Engl J Med 2001;344:1888–94.
31. Moliterno DJ, Topol EJ. A direct comparison of tirofiban and abciximab during percutaneous coronary revascularization and stent placement: rationale and design of the TARGET study. Am Heart J 2000;140:722–6.
32. Rao AK, Pratt C, Berke A, et al. Thrombolysis In Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.
33. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–81.
34. Assali AR, Salloum J, Sdringola S, et al. Effects of clopidogrel pretreatment before percutaneous coronary intervention in patients treated with glycoprotein IIb/IIIa inhibitors (abciximab or tirofiban). Am J Cardiol 2001;88:884–6, A6.
35. Steinhubl SR, Berger PB, Mann JT 3rd, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;288:2411–20.
36. Quinn MJ, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa inhibitors: recognition of a two-edged sword? Circulation 2002;106:379–85.
37. Harker LA, Marzec UM, Kelly AB, et al. Clopidogrel inhibition of stent, graft, and vascular thrombogenesis with antithrombotic enhancement by aspirin in nonhuman primates. Circulation 1998;98: 2461–9.
38. Herbert JM, Dol F, Bernat A, Falotico R, Lale A, Savi P. The antiaggregating and antithrombotic activity of clopidogrel is potentiated by aspirin in several experimental models in the rabbit. Thromb Haemost 1998;80:512–8.
39. Steinhubl SR, Talley JD, Braden GA, et al. Point-of-care measured platelet inhibition correlates with a reduced risk of an adverse cardiac event after percutaneous coronary intervention: results of the GOLD (AU-Assessing Ultegra) multicenter study. Circulation 2001;103: 2572–8.
40. Kabbani SS, Aggarwal A, Terrien EF, DiBattiste PM, Sobel BE, Schneider DJ. Suboptimal early inhibition of platelets by treatment with tirofiban and implications for coronary interventions. Am J Cardiol 2002;89:647–50.
41. Lakkis NM, George S, Thomas E, Ali M, Guyer K, Carville D. Use of ICHOR-platelet works to assess platelet function in patients treated with GP IIb/IIIa inhibitors. Catheter Cardiovasc Interv 2001;53:346–51.
42. Simon D, Liu G, Ganz P, et al. A comparative study of light transmission aggregometry and automated bedside platelet function assays in patients undergoing percutaneous coronary intervention and receiving abciximab, eptifibatide, or tirofiban. Catheter Cardiovasc Interv 2001;52:433–4.
43. Swieirkosz TA, Kapoor S, Tardiff DC, et al. Does greater platelet inhibition explain abciximab's superiority in the TARGET trial? A randomized comparison. Circulation 2001;104:II–385.
44. Chew DP, Bhatt DL, Robbins MA, et al. Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. Circulation 2001; 104:992–7.
45. Walter DH, Fichtlscherer S, Sellwig M, Auch-Schwelk W, Schachinger V, Zeiher AM. Preprocedural C-reactive protein levels and cardiovascular events after coronary stent implantation. J Am Coll Cardiol 2001;37:839–46.
46. Chew DP, Bhatt DL, Robbins MA, et al. Effect of clopidogrel added to aspirin before percutaneous coronary intervention on the risk associated with C-reactive protein. Am J Cardiol 2001;88:672–4.
47. Klinkhardt U, Graff J, Harder S. Clopidogrel, but not abciximab, reduces platelet leukocyte conjugates and P-selectin expression in a human ex vivo in vitro model. Clin Pharmacol Ther 2002;71:176–85.
48. Stone GW, Moliterno DJ, Bertrand M, et al. Impact of clinical syndrome acuity on the differential response to 2 glycoprotein IIb/IIIa inhibitors in patients undergoing coronary stenting: the TARGET trial. Circulation 2002;105:2347–54.